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(54) Title: COMBINATION THERAPY FOR TREATING ALZHEIMER'S DISEASE

(57) Abstract: The instant invention provides a drug combination comprised of an HMG-CoA reductase inhibitor in combination with a COX-2 inhibitor, which is useful for treating or preventing Alzheimer's disease.

TITLE OF THE INVENTION

COMBINATION THERAPY FOR TREATING ALZHEIMER'S DISEASE

BACKGROUND OF THE INVENTION

Alzheimer's disease is a neurodegenerative disease of the brain leading to severely impaired cognition and functionality. This disease leads to progressive regression of memory and learned functions. Alzheimer's disease is a complex disease that affects cholinergic neurons, as well as serotonergic, noradrenergic and other central neurotransmitter systems. Manifestations of Alzheimer's disease extends beyond memory loss and include personality changes, neuromuscular changes, seizures, and occasionally psychotic features.

Inhibitors of cyclooxygenase-2 are a sub-class of the class of drugs known as non-steroidal antiinflammatory drugs (NSAIDs). The NSAIDs are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process but are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandin by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway including the enzyme cyclooxygenase (COX). The recent discovery that there are two isoforms of the COX enzyme, the first, COX-1, being involved with physiological functions and the second, COX-2, being induced in inflamed tissue, has given rise to a new approach. While conventional NSAIDs block both forms of the enzyme, the identification of the inducible COX-2 enzyme associated with inflammation has provided a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects. Many compounds which have activity as COX-2 inhibitors have

been identified, including rofecoxib (VIOXX®), etoricoxib (ARCOXIA™), celecoxib (CELEBREX®), valdecoxib, parecoxib, and much research continues in this area.

HMG-CoA reductase inhibitors are a class of cholesterol-lowering agents and include lovastatin (MEVACOR®), simvastatin (ZOCOR®), pravastatin (PRAVACHOL®), fluvastatin (LESCOL®), atorvastatin (LIPITOR®) and cerivastatin (BAYCHOL).

This present invention provides for a method of treating, arresting the development of or preventing Alzheimer's disease employing an HMG-CoA reductase inhibitor and a cyclooxygenase-2 inhibitor. Epidemiological studies indicate inflammation is a factor leading to the progression of Alzheimer's disease. See Peter E. Lipsky, Am. J. Med., 1999; 106(5B):51S-57S, 1999. In addition, the use of COX-2 inhibitors for the treatment of neurodegenerative diseases, including Alzheimer's disease, is disclosed in United States Application Publication No. US2001/0016595 published on August 23, 2001, which is hereby incorporated by reference in its entirety. WO 95/06470, published on March 9, 1995, which is hereby incorporated by reference in its entirety, discloses the use of an HMG-CoA reductase inhibitor for the prevention or treatment of Alzheimer's disease.

SUMMARY OF THE INVENTION

The instant invention provides a novel drug combination comprised of an HMG-CoA reductase inhibitor in combination with a COX-2 inhibitor, useful for treating or preventing Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method for treating or preventing Alzheimer's disease in a human comprising administering to said human an HMG-CoA reductase inhibitor in combination with a cyclooxygenase-2 inhibitor in amounts that are effective to treat or prevent Alzheimer's disease.

A compound which inhibits HMG-CoA reductase is used in combination with a COX-2 inhibitor to practice the instant invention.

Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see US Patent No. 4,231,938), simvastatin (ZOCOR®; see US Patent No. 4,444,784), pravastatin (PRAVACHOL®; see US Patent No. 4,346,227), fluvastatin (LESCOL®; see US Patent No. 5,354,772), atorvastatin (LIPITOR®; see US Patent No. 5,273,995) and cerivastatin (BAYCHOL®, also known as rivastatin; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996). The term HMG-CoA reductase inhibitor is intended to include all pharmaceutically acceptable salt, ester and lactone forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters and lactone forms is included within the scope of this invention. Preferably, the HMG-CoA RI is selected from lovastatin and simvastatin, and most preferably simvastatin.

Herein, the term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base. Examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium,

stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

An embodiment of the invention encompasses the above method wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin and the pharmaceutically acceptable salt, ester and lactone forms thereof.

Another embodiment of the invention encompasses the above method wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

Another embodiment of the invention encompasses the above method wherein the HMG-CoA reductase inhibitor is simvastatin.

The terms "inhibitor of cyclooxygenase-2", "cyclooxygenase-2 inhibitor" and "COX-2 inhibitor" as used herein embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Employing the human whole blood COX-1 assay and the human whole blood COX-2 assay described in C. Brideau et al, Inflamm. Res. *45*: 68-74 (1996), herein incorporated by reference, preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 2 μM in the human whole blood COX-2 assay, yet have a cyclooxygenase-1 IC_{50} of greater than about 5 μM in the human whole blood COX-1 assay. Also preferably, the compounds have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 10, and more preferably of at least 40. The resulting selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

Examples of cyclooxygenase-2 selective inhibitors include rofecoxib (VIOXX®, see U.S. Patent No. 5,474,995), etoricoxib (ARCOXIA™ see U.S. Patent No. 5,861,419), celecoxib (CELEBREX®, see U.S. Patent No. 5,466,823), valdecoxib (see U.S. No. 6,633,272), parecoxib (see U.S. No. 5,932,598), COX-189 (Novartis), BMS347070 (Bristol Myers

Squibb), JTE522 (Japan Tobacco), ABT963 (Abbott), CS502 (Sankyo) and GW406381 (GlaxoSmithKline). Other examples of cyclooxygenase-2 inhibitors compounds are disclosed in U.S. Patent No. 6,020,343, which is hereby incorporated by reference, as follows:

(1) 3-(3,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(2) 3-(3-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(3) 3-(3 ,5-Difluorophenoxy)-5,5-dimethyl-4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(4) 3-Phenoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(5) 3-(2,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(6) 3-(4-Chlorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(7) 3-(3,4-Dichlorophenoxy)-5,5-dimethyl-4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(8) 3-(4-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(9) 3-(4-Fluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(10) 3-(3,5-Difluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(11) 3-Phenylthio-5,5-dimethyl-4(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(12) 3-(N-Phenylamino)-5,5-dimethyl-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(13) 3-(N-Methyl-N-phenylamino)-5,5-dimethyl-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(14) 3-Cyclohexyloxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(15) 3-Phenylthio-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(16) 3-Benzyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(17) 3-(3,4-Difluorophenylhydroxymethyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phen yl)-5H-furan-2-one,

(18) 3-(3,4-Difluorobenzoyl)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(19) 3-Benzoyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(20) 4-(4-(Methylsulfonyl)phenyl)-3-phenoxy-1-oxaspiro[4,4]non-3-en-2-one,

(21) 4-(4-(Methylsulfonyl)phenyl)-3-phenylthio-1-oxaspiro[4.4] non-3-en-2-one,

(22) 4-(2-Oxo-3-phenylthio-1-oxa-spiro[4,4]non-3-en-4-yl) benzenesulfonamide,

(23) 3-(4-Fluorobenzyl)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(24) 3-(3,4-Difluorophenoxy)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(25) 3-(5-Chloro-2-pyridyloxy)-5 ,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(26) 3-(2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(27) 3-(6-Methyl-2-pyridyloxy)-5,5-dimethyl4(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(28) 3-(3-Isoquinolinoxy)-5 ,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(29) 3-(4-(Methylsulfonyl)phenyl)-2-phenoxycyclopent-2-enone,

(30) 3-(4-(Methylsulfonyl)phenyl)-2-(3,4-difluorophenoxy) cyclopent-2-enone;

(31) 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(5-bromopyridin-2-yloxy)-5H-furan-2-one,

(32) 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

(33) 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

(34) 2-(3.4-difluorophenoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-enone,

(35) 3-(5-Benzothiophenyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(36) 5,5-dimethyl-4-(4-methlsulfonyl-phenyl)-3-(pyridyl-4-oxy)-5H-furan-2-one,

(37) 5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(pyridyl-3-oxy)-5H-furan2-one,

(38) 3-(2-Methyl-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(39) 3(2-Fluoro-4-trifluoromethyl)phenoxy-4-(4,-methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one,

(40) 3-(5-Chloro-2-pyridylthio)-5,5-dimethyl4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(41) 2-(3,5-Difluorophenoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-enone,

(42) 3-(2-Pyrnimdinoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(43) 3-(3-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(44) 3-(3-Chloro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(45) 3-(3-(1,2,5-thiadiazolyl)oxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one,

(46) 3-(5-Isoquinolinoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(47) 3-(6-Amino-2-pyridyloxy)-5,5-dimethyl4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(48) 3-(3Chloro -4-fluoro)phenoxy-4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one,

(49) 3-(6-Quinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

(50) 3-(5-Nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan- 2-one,

(51) 3-(2-Thiazolylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(52) 3-(3-Chloro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(53) 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one,

(54) 3-(3-Trifluoromethyl)phenoxy-4-(4-methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one,

(55) 5,5-Dimethyl-(4-(4-methylsulfonyl)phenyl)-3-(piperidine-1-carbonyl)-5-H-furan-2-one,

(56) 5,5-Dimethyl-3-(2-Butoxy)-4-(4-methylsulfonylphenyl)-5H-furan-2-one,

(57) 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(3-pentoxy)-5H-furan-2-one,

(58) 2-(5-Chloro-2-pyridyloxy)-3-(4-methylsulfonyl)phenylcycopent-2-enone,

(59) 3-(4-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(60) (5R)-3-(3,4-Difluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5 H-furan-2-one,

(61) (5R)-3-(4-Chlorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(62) 3-(2-Methyl-3-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(63) 3-(4-Methyl-5-nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(64) 3-(5-Chloro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(65) 3-(5-Fluoro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(66) 3-(3-Chloro-2-pyridyloxy)-5,5-dimethyl-4(4-methylsulfonyl)phenyl-5H-furan-2-one,

(67) 3-(4-Fluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-propyl-5H-furan-2-one,

(68) 3-(N,N-Diethylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)-phenyl)-5H-furan-2-one,

(69) 5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(3,5-dichloro-2-pyridyloxy)-5H-furan-2-one,

(70) (5R)-3-(4-Bromophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(71) (SR)-3-(4-Methylphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(72) (5R)-3-(5-Chloro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2, 2-difluoroethyl)-5H-furan-2-one,

(73) 3-(5-Chloro-2pyridyloxy)-5-methyl4-(4-methylsulfonyl)phenyl-5-propyl-5H-furan-2-one,

(74) 5-Methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-(propoxy)-5-(2-trifluoroethyl)- 5H-furan-2-one,

(75) S(R)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)5H-furan-2 -one,

(76) 5,5-dimethyl-3-(2,2-dimethylpropyloxy)-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(77) S(R) 3-(1-cyclopropyl-ethoxy)-5-ethyl-5-methyl4-(4-(methylsulfonyl)phenyl-5H-furan-2-one,

(78) 5(S) S-Ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl-3-(2-propoxy)-5H-furan-2-one,

(79) 3-(1-cyclopropyl-ethoxy)-5,5-dimethyl4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(80) 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(81) 5,5-dimethyl-3-(isobutoxy)-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(82) 3-(4-Bromophenoxy)-5,5-dimethyl-4(4-(methylsulfonyl)phenyl)-5H-furan-2-one

(83) 3-(2-Quinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

(84) 3-(2-Chloro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(85) 3-(6-benzothiazolyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(86) 3-(6-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(87) 3-(4-Quinazolyloxy)-5,,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(88) (5R)-3-(5-Fluoro-2-pyridyloxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(89) (5R)-3-(4-Fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(90) (5R)-3-(5-Fluoro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2, 2-trifluoroethyl)-5H-furan-2-one,

(91) 3-(1-Isoquinolinyloxy)-5,5-dimethyl-4-(methylsulfonyl)phenyl-5H-furan-2-one,

(92) (5R)-3-(4-fluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one,

(93) 3-(3-Fluoro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl) phenyl-5H-furan-2-one,

(94) (5R)-3-(3,4-difluorophenoxy)-5-mehtyl-4-(4-methylsulfonyl) phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one,

(95) (5R)-3-(5-chloro-2-pyridyloxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl -5H-furan-2-one,

(96) 3-(3,4-difluorophenoxy)-5-methyl-5-trifluoromethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(97) 3-(3,4-Difluorophenoxy)-5-methyl-4-(4-(methylsulfonyl)phenyl)-5-propyl-5H-furan-2-one,

(98) 3-Cyclobutyloxy-5,5-dimethyl-4-(4-methylsulfonylphenyl-5H-furan-2-one,

(99) 3-(1-Indanyloxy)-5,5-dimethyl4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(100) 3-(2-Indanyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one,

(101) 3-Cyclopentyloxy-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one,

(102) 3-(3,3-Dimethylcyclopentyloxy)-5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-5H -furan-2-one,

(103) 3-Isopropoxy-5-methyl-4-(4-methylsulfonyl phenyl)-5-propyl-5H-furan-2-one,

(104) 3-(2-Methoxy-5-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(105) 3-(5-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(106) (5RS)-3-(3,4-Difluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one,

(107) 3-(3-Chloro-4-methoxyphenoxy)-5,5-dimethyl-4-(4-methylsulfonyl)pheny-5H-furan-2-one,

(108) (5R)-3-(3-Chloro-4-methoxyphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(109) (5R)-3-(4Chlorophenoxy)-5-trifluoroethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(110) (5R)-3-(4-Bromophenoxy)-5-trifluoroethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(111) 5-Cyclopropylmethyl-3-(3,4-difluorophenoxy)-5-methyl-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(112) (5R)-3-(3-Fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(113) (5R)-3-(4-Chloro-3-fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(114) (5R)-3-Phenoxy-ethyl-5-methyl-4-(4-methIlsulfonyl)phenyl-5H-furan-2-one,

(115) (5R)-3-(4-Chloro-3-methylphenoxy)-5-ethyl-methyl-4-(4-methylsulfonyl)phenyl-5-furan-2-one,

(116) 3-(4-Chloro-3-methylphenoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(117) (5R)-3-(5-bromo-2 -pyridyloxy)-4-(4-methylsulfonylphenyl)-5-methyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one,

(118) (5R)-3-(5-bromo-2-pyridyloxy)-4-(4-methylsulfonylphenyl)-5-ethyl-(5-methyl-5H-furan-2-one,

(119) 3-(5-chloro-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(120) 3-(5-cyclopropyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(121) 3-(1-cyclopropylethoxy)-4-(4-methylsulfonyl)phenyl-5H-furan-2-one,

(122) 3-(cyclopropylmethoxy)-4-(4-methylsulfonyl)phenyl-5H-furan-2-one;

(123) (5S) 5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;

(124) (SR) 5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one; and
(125) (RS) 5-ethyl-5-methyl4(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one.

An embodiment of the invention encompasses the above method wherein the cyclooxygenase-2 inhibitor is selected from the group consisting of: rofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, COX-189, BMS347070, JTE522, ABT963, CS502 and GW406381.

Another embodiment of the invention encompasses the above method wherein the cyclooxygenase-2 selective inhibitor is rofecoxib.

Another embodiment of the invention encompasses the above method wherein the cyclooxygenase-2 selective inhibitor is etoricoxib.

The compounds of use in this invention may have one or more chiral centers and the present compounds may occur as racemates, racemic mixtures and as individual diasteriomers or enantiomers with all such isomeric forms and mixtures thereof being included within the scope of this invention. Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates and hydrates, as well as anhydrous compositions, are encompassed within the scope of this invention. Some of the compounds described herein may contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The COX-2 inhibitors that may be used with this invention encompass all pharmaceutically acceptable salt forms of the compounds. Examples of such salt forms of COX-2 inhibitors include but are not limited to salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary,

and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

The instant pharmaceutical combination comprising an HMG-CoA reductase inhibitor in combination with a COX-2 inhibitor includes administration of a single pharmaceutical dosage formulation which contains both the HMG-CoA reductase inhibitor and the COX-2 inhibitor, as well as administration of each active agent in its own separate pharmaceutical dosage formulation. Where separate dosage formulations are used, the HMG-CoA reductase inhibitor and the COX-2 inhibitor can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially. The instant pharmaceutical combination is understood to include all these regimens. Administration in these various ways are suitable for the present invention as long as the beneficial pharmaceutical effect of the HMG-CoA reductase inhibitor and the COX-2 inhibitor are realized by the patient at substantially the same time. Such beneficial effect is preferably achieved when the target blood level concentrations of each active drug are maintained at substantially the same time. It is preferred that the HMG-CoA reductase inhibitor and the COX-2 inhibitor be co-administered concurrently on a once-a-day dosing schedule; however, varying dosing schedules, such as the HMG-CoA RI once per day and the COX-2 inhibitor once, twice or more times per day, is also encompassed herein. A single oral dosage formulation comprised of both an HMG-CoA reductase inhibitor and the COX-2 inhibitor is preferred. A single dosage formulation will provide convenience for the patient, which is an important consideration especially for patients who already have coronary heart disease and may be in need of multiple medications.

The term "amounts that are effective to treat or prevent" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The present invention encompasses not only treating a patient who displays symptoms of Alzheimer's disease but also preventing the onset or progression of the disease. The dosage regimen utilizing an HMG-CoA RI in combination with COX-2 inhibitor is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt or ester thereof employed. Since two different active agents are being used together in a combination therapy, the potency of each of the agents and the interactive effects achieved by combining them together must also be taken into account. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amounts needed to prevent, counter, or arrest the progress of the condition.

The term "patient" means humans who take an HMG-CoA reductase inhibitor in combination with a COX-2 inhibitor for any of the uses described herein. Administering of the drug combination to the patient includes both self-administration and administration to the patient by another person.

In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor are intended to be the same or similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the Physicians' Desk Reference (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. Preferably, the oral dosage amount of HMG-CoA RI is from about 1 to 200 mg/day, and more preferably from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-

CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA RI which has sufficiently greater potency may be given in sub-milligram daily dosages. The HMG-CoA reductase inhibitor may be administered from 1 to 4 times per day, and preferably once per day.

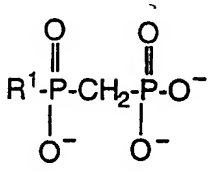
As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg; for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; for pravastatin sodium, 10 mg, 20 mg, and 40 mg; and for atorvastatin calcium, 10 mg, 20 mg, and 40 mg.

The inhibitor of cyclooxygenase-2 may be administered at a dosage level up to conventional dosage levels for NSAIDs. Suitable dosage levels will depend upon the antiinflammatory effect of the chosen inhibitor of cyclooxygenase-2, but typically suitable levels will be about 0.001 to 50 mg/kg per day, preferably 0.005 to 30mg/kg per day, and especially 0.05 to 10mg/kg per day. The compound may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, and especially once per day.

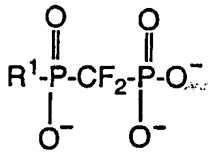
Additional active agents may be used in combination with the HMG-CoA RI and COX-2 inhibitor in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration. One or more additional active agents may be administered with the HMG-CoA RI and COX-2 inhibitor. The additional active agent or agents can be cholesterol lowering compounds. Examples of additional active agents which may be employed include HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrizol; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); beta-blockers; folic acid or a pharmaceutically

acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

Examples of HMG-CoA synthase inhibitors include: the beta-lactone derivatives disclosed in U.S. Patent No. 4,806,564, 4,816,477, 4,847,271, and 4,751,237; the beta lactam derivatives disclosed in U.S. 4,983,597 and the substituted oxacyclopropane analogues disclosed in European Patent Publication EP O 411 703. The squalene synthetase inhibitors suitable for use herein include, but are not limited to, those disclosed by Biller et al., J. Med. Chem., 1988 Vol. 31, No. 10, pp. 1869-1871, including isoprenoid (phosphinylmethyl)-phosphonates such as those of the formula

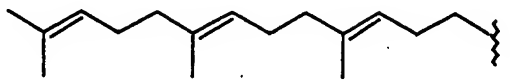


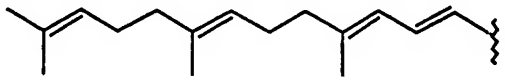
I

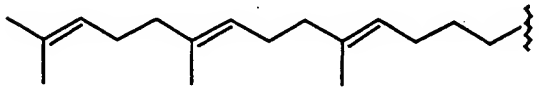


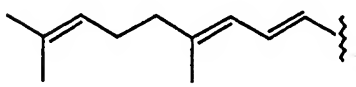
II

wherein R^1 is:

a 

b 

c 

d 

including the triacids thereof, triesters thereof and tripotassium and trisodium salts thereof as well as other squalene synthetase inhibitors disclosed in pending U.S. Patent No. 4,871,721 and 4,924,024 and in Biller et al., J. Med.Chem., 1988, Vol. 31, No. 10, pp. 1869 to 1871.

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al., J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc. 1976, 98, 1291-1293, phosphinylphosphonate reported by McClard, R. W. et al., J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U. of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary.

Further, the benzodiazepine squalene synthase inhibitors described in EP O 567 026 to Takeda Chemical Industries, and the quinuclidinyl squalene synthase inhibitors described in PCT publications WO 94/03451, WO 93/09115, WO 93/21183, WO 93/21184, WO 93/24486, and U.S. 5,135,935, may be co-administered with the HMG-CoA RI plus COX-2 inhibitor combination of the present invention. In addition, the zaragozic acid type squalene synthase inhibitors as described in U.S. Patents 5,284,758; 5,283,256; 5,262,435; 5,260,332; 5,264,593; 5,260,215; 5,258,401; 5,254,727; 5,256,689; 5,132,320; 5,278,067, and PCT Publications WO 92/12156; WO 92/12157; WO 92/12158; WO 92/12159; WO 92/12160; WO 93/18040; WO 93/18039; WO 93/07151; and European Patent Publications EP O 512 865, EP O 568 946; EP O 524,677 and EP O 450 812, as well as the acyclic tricarboxylic acid compounds of U.S. patent 5,254,727, may be employed.

Illustrative examples of squalene epoxidase inhibitors are disclosed in European Patent Publication EP O 318 860 and in Japanese Patent Publication JO2 169-571A. LDL-receptor gene inducer molecules are disclosed in U.S. Patent No. 5,182,298.

Examples of bile acid sequestrants which may be employed in the present method include cholestyramine, colestipol, and poly[methyl-(3-

_ethylaminopropyl)imino-trimethylene dihalide] and those disclosed in =95/34585 to Geltex Pharmaceuticals, Inc. and EP 0 622 078 assigned _isamitsu Pharmaceutical Co., Inc.

Examples of cholesterol absorption inhibitors which may be _loyed in the present method include those described in WO 95/18143 WO 95/18144 both assigned to Pfizer Inc., and WO 94/17038, WO 8532 and WO 93/02048 each assigned to Schering Corp.

The additional active agents described above which may be _loyed along with the HMG-CoA RI and COX-2 inhibitor combination _apy can be used, for example, in amounts as indicated in the PDR or =mounts as indicated in the reference disclosures, as appropriate.

The active agents employed in the instant combination _apy can be administered in such oral forms as tablets, capsules (each hich includes sustained release or timed release formulations), pills, =lers, granules, elixirs, tinctures, suspensions, syrups, and emulsions. instant invention includes the use of both oral rapid-release and time- =rolled release pharmaceutical formulations. A particular example of =ral time-controlled release pharmaceutical formulation is described in Patent No. 5,366,738. Oral formulations are preferred. Such =maceutical compositions are known to those of ordinary skill in the =maceutical arts; for example, see Remington's Pharmaceutical =nces, Mack Publishing Co., Easton, PA.

In the methods of the present invention, the active agents are =ally administered in admixture with suitable pharmaceutical =nts, excipients or carriers (collectively referred to herein as "carrier" =erials) suitably selected with respect to the intended form of =inistration, that is, oral tablets, capsules, elixirs, syrups and the like, consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or =ule, the active drug component can be combined with a non-toxic, =maceutically acceptable, inert carrier such as lactose, starch, sucrose, ose, modified sugars, modified starches, methyl cellulose and its =vatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and =r reducing and non-reducing sugars, magnesium stearate, steric acid,

sodium stearyl fumarate, glyceryl behenate, calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring and flavoring agents can also be incorporated into the mixture. Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) can also be added to stabilize the dosage forms. Other suitable components include gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, carboxymethylcellulose, polyethylene glycol, waxes and the like.

The active drugs can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

Although the active agents of the present method may be administered in divided doses, for example two or three times daily, a single daily dose of each of the HMG-CoA RI and the COX-2 inhibitor is preferred, with a single daily dose of both agents in a single pharmaceutical composition being most preferred.

The instant invention also encompasses a process for preparing a pharmaceutical composition comprising combining the HMG-CoA RI and the COX-2 inhibitor with a pharmaceutically acceptable carrier, as well as the pharmaceutical composition which is made by combining the HMG-CoA RI and the COX-2 inhibitor with a pharmaceutically acceptable carrier.

A therapeutically effective amount of an HMG-CoA RI and a COX-2 inhibitor can be used together for the preparation of a medicament useful for treating or preventing Alzheimer's disease. For example, the medicament may be comprised of a COX-2 inhibitor in combination with about 1 mg to 200 mg of an HMG-CoA RI, or more particularly about 5 mg to 160 mg of the HMG-CoA RI. More specific amounts of HMG-CoA RI which may be used in the medicament preparation include 1 mg, 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg, as well as sub-milligram amounts of HMG-CoA RI's which have sufficient potency at such levels. As a further example, the medicament may be comprised of an HMG-CoA RI in combination with about 0.1 to 20 mg of a COX-2 inhibitor.

The instant invention also encompasses the use of an HMG-CoA reductase inhibitor for the preparation of a medicament for the combined use with a cyclooxygenase-2 inhibitor for treating Alzheimer's disease; and the use of a cyclooxygenase-2 inhibitor for the preparation of a medicament for the combined use with an HMG-CoA reductase inhibitor for treating or preventing Alzheimer's disease. The medicament or pharmaceutical combination comprised of the HMG-Co RI and the COX-2 inhibitor may also be prepared with one or more additional active agents, such as those described supra.

WHAT IS CLAIMED IS:

1. A method for treating or preventing Alzheimer's disease in a human comprising administering to said human an HMG-CoA reductase inhibitor in combination with a cyclooxygenase-2 inhibitor in amounts that are effective to treat or prevent Alzheimer's disease.

2. The method according to Claim 1 wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin and the pharmaceutically acceptable salt, ester and lactone forms thereof.

3. The method according to Claim 2 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

4. The method according to Claim 3 wherein the HMG-CoA reductase inhibitor is simvastatin.

5. The method according to Claim 1 wherein the cyclooxygenase-2 inhibitor is selected from the group consisting of: rofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, COX-189, BMS347070, JTE522, ABT963, CS502 and GW406381.

6. The method according to Claim 5 wherein the cyclooxygenase-2 selective inhibitor is rofecoxib.

7. The method according to Claim 5 wherein the cyclooxygenase-2 selective inhibitor is etoricoxib.

8. The method according to Claim 1 further comprising the administration of a therapeutically effective amount of at least one additional active agent selected from an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, a squalene synthetase inhibitor, an ACAT inhibitor, probucol, niacin, a fibrate, a cholesterol absorption inhibitor, a

bile acid sequestrant, an LDL receptor inducer, a platelet aggregation inhibitor, vitamin B_6 and the pharmaceutically acceptable salts thereof, vitamin B_{12}, a beta-blocker, folic acid or a pharmaceutically acceptable salt or ester thereof, vitamin C, vitamin E and beta carotene.

9. A method for treating or preventing Alzheimer's disease in a human comprising administering to said human simvastatin in combination with rofecoxib in amounts that are effective to treat or prevent Alzheimer's disease.

10. A method for treating or preventing Alzheimer's disease in a human comprising administering to said human simvastatin in combination with etoricoxib in amounts that are effective to treat or prevent Alzheimer's disease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US02/32790

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/42, 31/50, 31/196, 31/216, 31/341, 31/351, 31/405, 31/415, 31/421, 31/505, 31/4418
US Cl. : 514/247, 277, 275, 334, 374, 378, 406, 415, 460, 473, 548, 567

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/247, 277, 275, 334, 374, 378, 406, 415, 460, 473, 548, 567

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database CAPLUS on STN, AN 135:56086, WALDSTREICHER, J. 'Cyclooxygenase 2 inhibitor-HMG-CoA reductase inhibitor combination for treating neurodegenerative diseases, especially Alzheimer's disease'. WO 2001045698 A1, 28 June 2001.	

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents.

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2003 (17.04.2003)	23 APR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer PHYLLIS SPIVACK Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)